REMARKS

As stated in the Supplemental Office Action, claims 1–28 are pending in this application. In this amendment, claims 9-13 are amended and claims 14-28 have been withdrawn from consideration as directed to non-elected subject matter. Applicants reserve the right to file a continuation or divisional application on any subject matter withdrawn by way of this amendment. Applicants respectfully request consideration of the subject application as amended herein.

The amendments to the claims do not introduce new subject matter.

Applicant acknowledges the Examiner's designation of the priority date April 9, 1999 for the claims.

Specification

The Examiner has requested a new title "that is clearly indicative of the invention to which the elected claims are directed." The Examiner states that "the title is directed to nucleic acids and amino acids[,]" but the "claims are drawn to nucleic acids[.]" The pending claims are directed to nucleic acid sequences which encode amino acid sequences. Further, these amino acid sequences are disclosed in the specification. Claim 1 is directed to nucleic acid that encodes for an amino acid sequence. Thus, claim 1 includes a polypeptide described in the specification and encoded by a nucleic acid sequence of Applicants' invention and therefore, Applicants believe it is unnecessary to modify the title.

Amendments to the Claims

Claim 9 has been as amended to recite "a nucleotide sequence comprising at least twenty consecutive nucleotides[.]" Support for amendments to claim 9 can be found in the Specification, for example, at page 11, lines 18-25.

Claim 10 has been as amended to recite "a nucleotide sequence of at least forty nucleotides[.]" Support for amendments to claim 10 can be found in the Specification, for example, at page 11, lines 18-25.

Claims 11-13 have been as amended to recite "an immunogenic composition[.]" Support for amendments to claims 11-13 can be found in the Specification, for example, at page 65, line 1 to page 68, line 4.

The amendments to the above claims have been made without prejudice or disclaimer. Applicants reserve the right to pursue the canceled subject matter in a divisional and/or continuation application.

I. Rejection of Claims 1-13 Under 35 U.S.C. § 101

The Examiner has rejected Claims 1-13 under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by either specific, substantial or a well established utility.

Applicants assert that a well-established utility and a specific, substantial, and credible utility have been established for the claimed invention. At a minimum, the elected sequences and the compositions of the present invention may be used as molecular targets for identification of new antimicrobials agents, probes for diagnostic assays, and targets for vaccine development. See Exhibits 1, 2, and 3.

The Manual of Patent Examining Procedure (MPEP) states at § 2107.01, that research tools can be "useful" in a patent sense:

> Many research tools such as . . . nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

Therefore, nucleotide sequencing techniques, which can include microbial genomic databases containing nucleic acid sequences, amino acid sequences and sequence homology information of bacterial genes that are, in turn, useful in the functional analysis of the bacterial genome, can meet the utility requirement of 35 U.S.C.§ 101 if, for example, the nucleic acid sequences and proteins encoded by the nucleic acid sequences have a well-established utility or, in the alternative, a specific, substantial, and credible

utility such as in the development of antibiotics, diagnostics, vaccines, and drugs to treat humans afflicted with infection caused by the bacteria.

I. The Specification Asserts A Well-Established Utility For The Claimed Invention

The MPEP states, at § 2107.02B, that the utility of 35 U.S.C. § 101 is met, even if a specific, substantial, and credible utility for the claimed invention is not asserted in the Specification, if such utility is well-established:

> An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

The guidelines for examination of patent applications under 35 U.S.C. § 101, "utility" requirement referenced by the Examiner, as shown in the Federal Register, Vol. 66, No. 4, pages 1092-1099, at page 1095, state:

> By statute, a patent is required to disclose one practical utility. If a well-established utility is readily apparent, the disclosure is deemed to be implicit.

The Federal Register, Vol. 66, No. 4, page 1097 also states:

> Only one specific, substantial and credible utility is required to satisfy the statutory requirement. Where one or more well-established utilities would have been readily apparent to those of skill in the art at the time of the invention, an [A]pplicant may rely on any one of those utilities without prejudice. (emphasis added).

The invention involves nucleic acid and amino acid sequences relating to *Bacteroides fragilis*. Many sources written by those skilled in the biological sciences describe the utility of sequence information from microbial pathogens as well-established in the art. For example, as shown in Exhibit 1, Moir, D.T., *et al., Antimicrob. Agents Chemother. 43:* 439-446 (1999), states, on page 439, that genomic sequence information has provided a wealth of information useful to assist in the development of strategies for antimicrobial drug discovery:

> [H]igh-throughput automated random genomic DNA sequencing together with robust fragment assembly tools has delivered a

> wealth of genomic sequence information to assist in the search for new targets. In many cases, entire biochemical pathways can be reconstructed and compared in different pathogens.

Further, Moir *et al.,* states, on page 440-441, that essential genomic sequence information is useful in identifying potential targets for new antimicrobials:

> Genes which are essential to pathogenesis and prevent colony formation in a conditional-lethal manner are potential targets for new antimicrobials.

In addition, Tatusov, R.L., *et al., Science 278:* 631-637 (1997), Exhibit 2, on page 631, states that comparisons of complete genomic sequences of bacteria are useful and can be critically important to the development of targets for new antibiotics:

> With multiple genome sequences, it is possible to delineate protein families that are highly conserved in one domain of life but are missing in the others. Such information may be critically important: For example, the families that are conserved among bacteria but are missing in eukaryotes comprise the pool of potential targets for broad-spectrum antibiotics.

Smith, D.R., *TIBTECH 14*: 290-293(1996), Exhibit 3, states, on pages 291-292, that the first task in identifying new strategies for therapeutics and vaccine targets is to identify genes of the microbial organism and that the second task is identifying sequence homology which is useful in the analysis of gene products. Specifically, Smith states on page 292:

> The second phase in the analysis of bacterial genomes is to identify the function of as many genes as possible. Currently, sequence homology is the most powerful tool. A high degree of homology between the putative translation product of a newly identified gene and an enzyme whose function has been thoroughly studied in other organisms, provides strong support for the function of that protein.

In addition, Smith states, on page 293, that microbial genome sequence information is useful in new strategies for identifying drug or vaccine development targets by targeting essential genes:

> The techniques described in the previous section can be used to identify genes in specific functional categories that may represent good targets for drug or vaccine development. In general, when developing new antibiotics, one is interested in genes that are essential under all growth conditions . . . .

Furthermore, the Specification discloses additional well-established utilities of the *B. fragilis* nucleotide sequences. For example, the nucleotide sequences can be useful for developing probes used in diagnostics to detect the presence of the *B. fragilis* pathogen. See Specification, page 31, lines 4-20. The nucleotide sequences can be useful for creating primers to amplify *B. fragilis* nucleic acids sequences. See Specification, page 32, lines 5-27. The nucleotide sequences are useful for the creation of antisense agents, which can be used to prevent the expression of *B. fragilis* genes. See Specification, page 33, lines 1-20.

The usefulness of the claimed invention includes providing information to assist in new drug discoveries, assisting in the development of targets for new antibiotics, and identifying new drug or vaccine development targets. The claimed invention can also be used as a means of diagnosing a patient or a biological sample with *B. fragilis*. These uses are apparent and implied by the Specification when taken with knowledge of one skilled in the art at the time of Applicants' invention. The claimed invention has a well-established utility. Thus, Applicants respectfully request the withdrawal of the 35 U.S.C. §101 rejection.

II. The Specification Asserts A Credible, Specific, And Substantial Utility For The Claimed Invention

A. <u>The claimed sequences have a specific utility.</u>

The Examiner states that:

> [t]he claimed nucleic acids, polynucleotides, vectors, host cells containing same, methods of expression of nucleic acids and as vaccine compositions are not supported by a specific asserted utility because the disclosed use of the nucleic acid is not specific and is generally applicable to any nucleic acid isolated from *B. fragilis*.

The MPEP states at § 2107.01 that a specific utility is:

> A "specific utility" is specific to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of invention. . . . [T]he situation where an [A]pplicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the . . .

category are sufficient to identify a specific utility for the invention.

In the Specification, Applicants have shown in Table 2 that SEQ ID NO:4084, which encodes for the polypeptide SEQ ID NO:9306, is a homolog of dnaB in *Rhodothermus mariuns*. According to Jezewska (Exhibit 4), "[t]he DnaB protein is an essential replication protein . . . which is involved in both the initiation and elongation stages of DNA replication[.]" (J. Biol. Chem. 273(15):9058-69 (1998)). DnaB is "the *E. coli* primary replicative helicase[,]" and it is "the only helicase required to reconstitute DNA replication *in vitro* from the chromosomal origin of replication." *Id.* at 9058.

Applicants provide results below from sequence alignments for the claimed invention with the dnaB reference sequence listed in Table 2 of the Specification. The summary table provides the claimed nucleotide SEQ ID NO. in the first column and the corresponding amino acid SEQ ID NO. in the second column. The description of the gene is in the third column and the protein name in the fourth column. The accession number of the reference sequence is in the fifth column. The percent identity between the reference sequence and the claimed sequence is provided in the sixth column.

In addition to the summary table below, the sequence alignment itself is submitted as Exhibit 5 to visually reinforce that the claimed sequence is a homolog of the reference sequence, dnaB. Applicants note that the accession number for nucleic acid is Y13813 and the corresponding protein is accession number 2661771. Exhibit 5 shows a sequence alignment with SEQ ID NO:9306 and accession number 2661771. These results were produced using the GCG Best Fit algorithm, which makes an optimal alignment between segments of sequences based on similarity.

Summary Table of Sequence Alignments and
Table 2 of Specification

Claimed Nucleotide SEQ ID NO:	Corresponding Amino Acid SEQ ID NO:	Description	Protein name	Accession Number	Percent Identity
4084	9306	*Rhodothermus mariuns* dnaB gene	RNDNAB	Y13813	45

These sequence alignments demonstrate a high degree of identity and similarity between the claimed sequence and the reference sequence from Table 2 of the Specification. By way of explanation of sequence alignment accuracy, Applicants submit the reference (Exhibit 6) by Rost, Protein Engineering, 12:85-94 (1999). Rost discloses that the accuracy of the results of sequence alignments is much higher when the sequence identity percentage is greater than 35%, because the number of false positives is drastically reduced at this point. A sequence identity higher than 35% is an accurate result. See Rost, pages 91-92.

Applicants note that the alignment of the claimed sequence yields a sequence identity of 45% which is over the 35% threshold suggested by Rost. Applicants point to the paragraph at the bottom of the first column of page 92 of the Rost publication, wherein Rost states that "[f]rom 100-35% sequence identity, any residue exchange resulting in a stable structure maintains structure."

Moreover, Exhibit 7 shows multiple dnaB sequence alignments across multiple bacterial species. The multiple sequence alignments were performed using the program ClustalW (Version 1.83). The dnaB protein sequences are from the bacteria *Rhodothermus marinus* (ac:Y13813; gi: 2661771), *Bacillus stearothermophilus* (ac:AF106032; gi:4416321), *Pseudomonas putida* (ac:AF229444; gi:12642370), and *Thermus aquaticus* (ac:AF100420; gi:4406210). The alignments show that conserved residues are shared among the polypeptide sequences of the dnaB protein across the various bacteria species. Exhibit 7 provides evidence that the present claimed sequence

and the dnaB proteins share similar functional domains. Thus, one of ordinary skill in the art would find the claimed sequence to be the dnaB gene for *B. fragilis*.

In addition, the conserved residues are patterned to form highly conserved functional domains across the bacterial species for the dnaB protein. These functional domains can be used in the screening of novel broad spectrum antibiotics across bacterial species. According to the Jezewska article, it was well known in the art at the time of filing the application that "[t]he dnaB protein is an essential replication protein . . . ." (J. Biol. Chem. 273(15):9058-69 (1998)). Essential genes are known to be useful for novel antibiotic screening and in the development of diagnostic kits as well as for other uses described by Moir *et al.*, Tatusov *et al.*, and Smith.

Applicants' claimed invention provides nucleic acid sequences which encode for important polypeptides used in diagnostics and therapeutics. Specifically, Applicants' claimed invention includes a wide variety of nucleic acid sequences which encode proteins that share homology with known proteins that have utility, several of which have been shown to be essential to the life of cell. Thus, the claimed invention has a specific utility.

B. The claimed sequences have a substantial utility.

The Examiner states that "the claimed nucleic acid is not supported by a substantial utility because no substantial utility has been established for the claimed subject matter."

The MPEP states at § 2107.01 that a substantial utility is defined as a utility that "defines a 'real world' use." For example, "a therapeutic method of treating a known or newly discovered disease . . . that themselves have a 'substantial utility' define a 'real world' context of use." *Id.* Given the important applications described in Moir *et al.*, Tatusov *et al.*, and Smith, Applicants submit that the development of treatments for bacterial infections constitute a "real world" use. Therefore, the presently claimed invention provides a satisfactory substantial utility.

C. The claimed sequences have a credible utility.

Regarding credible utility, according to the MPEP at § 2107.01, "in view of the rare nature of such cases, Office personnel should not label an asserted utility 'incredible,' 'speculative' or otherwise unless it is clear that a rejection based on 'lack of utility' is proper." A credible utility is "assessed from the perspective of one of ordinary skill in the art, in view of the disclosure and any other evidence of record that is probative of the [A]pplicants assertions." Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001). The claimed sequences can be used as probes, capture ligands, primers, antisense agents, or diagnostic markers for the detection of specific disease causing pathogens. See Specification, page 31, line 4 to page 33, line 20. The relationship of the claimed nucleic acid sequences and corresponding amino acid sequences to essential genes of other pathogens with clearly, defined functions and usefulness demonstrate that an Examiner would have no reason to dismiss the asserted utility as incredible or speculative. Thus, the claimed invention has a credible utility.

D. Conclusion

Because the claimed invention has a well-established and a specific, substantial, and credible utility, it meets the requirements of 35 U.S.C. § 101. Thus, Applicants respectfully request the withdrawal of the 35 U.S.C. §101 rejection.

II. Rejection of Claims 1-13 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-13 under U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' argument *supra* demonstrates that the claimed invention is supported by a specific, credible, and substantial utility and a well-established utility. Accordingly, Applicants respectfully request the removal of the U.S.C. § 112, first paragraph rejection.

III. Rejection of Claims 11-13 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 11-13 under 35 U.S.C. § 112, first paragraph, as further not enabling for vaccines in the treatment or prevention of a *B. fragilis* infection.

Applicants do not agree and note that the claimed sequences do enable the development of vaccines to treat or prevent *B. fragilis* infections. However to expedite prosecution, claims 11-13 have been amended to recite the term "immunogenic composition". Applicants reserve the right to pursue the subject matter in a divisional and/or continuation application.

IV. Rejection of Claims 9-10 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 9-10 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

Applicants respectfully traverse. As stated on page 1102 of the Federal Register, Vol. 66, No. 4, disclosure of a single species can provide an adequate written description of a generic claim, if one skilled in the art would recognize that the disclosure of the species includes the genus:

> The Guidelines now indicate that a single species may, in some instances, provide an adequate written description of a generic claim when the description of the species would evidence to one of ordinary skill in the art that the invention includes the genus.

A disclosure "is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz,* 124 U.S.P.Q. 449, 502 (C.C.P.A. 1960).

The Specification as filed provides ample support for the Claims. Literal support for claims 9-10 can be found in the Specification as filed on page 11, lines 18-25. The Specification states that:

> the nucleic acid which encodes an *B. fragilis* polypeptide of the invention, hybridizes under stringent conditions to a nucleic acid probe corresponding to . . . at least about 20 consecutive

> nucleotides of the invention contained in the Sequence Listing; most preferably to at least about 40 consecutive nucleotides . . . .

Prior to the filing of this patent application, functional domains of the dnaB protein in other species were well known in the art. For example, in 1998, Jezewska et al. published the following functional domain for the dnaB gene, which encodes the polypeptide helicase dnaB protein (J. Biol. Chem. 273(15):9058-69 (1998)). Jezewska states that:

> Fluorescence energy transfer experiments provide direct proof that the DnaB hexamer binds ssDNA in a single orientation, with respect to the polarity of the sugar-phosphate backbone. This is the first evidence of directional binding to ssDNA of a hexameric helicase in solution. The strong binding subsite is close to the small 12-kDa domains of the DnaB hexamer and occludes the 5'-end of the ssDNA. The strict orientation of the helicase on ssDNA indicates that, when the enzyme approaches the replication fork, it faces double-stranded DNA with its weak subsite. The data indicate that the different binding subsites are located sequentially, with the weak binding subsite constituting the entry site for double-stranded DNA of the replication fork. *Id.* at 9058.

Because functional domains for the dnaB gene are well known in the art, one of ordinary skill in the art is able to identify and utilize a probe or an isolated nucleic acid of at least 20 nucleotides selected from the group consisting of: (a) SEQ ID NO: 4084 (b) a complement of SEQ ID NO: 4084 or (c) an RNA of (a) or (b), wherein U is substituted for T. Moreover, this functional domain could be used in the screening of novel broad spectrum antibiotics across bacteria species.

Lastly, the Applicants wish to point out that SEQ ID NO:4084 is a full length gene, not a fragment. As indicated in the Specification on page 47, lines 21-23, SEQ ID NO:4084 is a full open reading frame or ORF. Thus, SEQ ID NO:4084 is not a fragment of a full length gene or cDNA. It can be incorporated into a living cell to manufacture or produce a full-length *B. fragilis* protein.

Accordingly, Applicants respectfully submit that the invention as described in the Specification as filed shows that the Applicants have possession of the claimed invention under 35 U.S.C. § 112 and respectfully request the withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

V. Rejection of Claims 9-10 Under 35 U.S.C. § 102

The Examiner has rejected claims 9-10 under 35 U.S.C. 102(e) as being anticipated by Ratti *et al.* ("Ratti"). The Examiner states that "Ratti *et al.* teach nucleic acids . . . comprising a nucleotide sequence of at least eight nucleotides in length . . . wherein the sequence is hybridizable to a nucleic acid having a nucleotide sequence of SEQ ID NO:4084."

This rejection, insofar as it applies to the claims as amended, is respectfully traversed, however, Applicants have amended claim 9 to state "at least twenty contiguous nucleotides" to expedite prosecution. Applicants have also amended claim 10 to state "at least forty nucleotides" for the same reason . Applicants reserve the right to pursue the subject matter of these claims in a divisional and/or continuation application.

Accordingly, Applicants respectfully submit that the invention as described in the specification shows that the Applicants' invention is distinguishable from that of Ratti and respectfully request the withdrawal of the rejection under 35 U.S.C. § 102(e).

SUMMARY AND CONCLUSION

Applicants' claimed invention, as amended, meets the requirements of 35 U.S.C. §§ 101, 102, and 112, first paragraph.

Reconsideration and withdrawal of the pending rejections are respectfully requested. If the Examiner feels that a telephone conference would expedite prosecution of this application, he is invited to call the undersigned at (781) 398-2548.

Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 501040.

Respectfully submitted,

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Dated: 5/13/03

Marked-up version of Claims

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

9. (Twice Amended) A probe comprising a nucleotide sequence consisting of at least twenty [eight] contiguous nucleotides of a nucleotide sequence selected from the group consisting of:

(a) SEQ ID NO: 4084;

(b) a complement of SEQ ID NO: 4084; or

(c) an RNA of (a) or (b), wherein U is substituted for T.

10. (Thrice Amended) An isolated nucleic acid comprising a nucleotide sequence of at least forty [eight] nucleotides in length, wherein the sequence is hybridizable to a nucleic acid having a nucleotide sequence selected from the group consisting of:

(a) SEQ ID NO: 4084;

(b) a complement of SEQ ID NO: 4084; or

(c) an RNA of (a) or (b), wherein U is substituted for T.

11. (Amended) An immunogenic [vaccine] composition for prevention or treatment of an *B. fragilis* infection comprising a nucleic acid of Claim 5 and a pharmaceutically acceptable carrier.

12. (Amended) An immunogenic [vaccine] composition of Claim 11, further comprising an adjuvant.

13. (Amended) An immunogenic [vaccine] composition of Claim 11, further comprising one or more additional [ingredients] components.